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EXAMINER
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ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,298	GALZI ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14* is/are pending in the application.

4a) Of the above claim(s) *14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Restriction Requirement:

Applicants' election, without traverse, of Group I, claims 1-12, drawn to a process for detecting an allosteric effector of a receptor, in the reply filed on 3 April 2008 is acknowledged. Applicants have canceled claim 13, and have presented new claim 14 which has been made of record.

Applicants assert that newly presented claim 14 is a product-by-process claim and is thus examinable with the elected group. Applicant's argument has been fully considered but are not found to be persuasive for the following reasons: Newly presented claim 14 is directed to the same products as recited in canceled claim 13 and would have been grouped with Group II. Claim 14 recites compounds as detected by the process of claim 1. A product detected by a process does not constitute a product made by, or used in the process of Group I. Thus, Claim 14 will not be included with the claims of Group I.

The requirement is still deemed proper and is therefore made **FINAL**.

Claims 1-12, and 14 are pending in the instant application. Claim 14 has been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-12 are under consideration.

Priority:

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in France on 17 June 2002. Receipt is acknowledged of French application 02/07436 which papers have been placed of record in the file. It is noted that no English translation of French application 02/07436 has been filed. Therefore, for purposes of prior art, priority is granted to 16 June 2003, the filing of PCT/FR03/01817.

Objections

Drawings:

The drawings are objected to because Figure 3 is undecipherable, being various shades of grey. Thus, the information conveyed in that figure cannot be evaluated. No columns with hatch marks are shown in the figures.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claims:

Claims 1-12 are objected to because of the following informalities: The claims would be more grammatically correct if the independent claims were amended to read, for example, " A process…." , and the dependent claims were amended to read "The process according to claim…."

Rejections

35 U.S.C. § 112, Second Paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2, the independent claims of the instant invention are incomplete method claims. To be complete, a method claim must state a goal in the preamble of the claim, and conclude having achieved that goal. Claims 1 and 2 are directed to a process for detection an allosteric effector. However, the method steps, as recited, are insufficient to accomplish the goal stated in the preamble. The method steps recite determination of the variation in the dissociation and/or association kinetics of the complex formed between the receptor and one of its ligands in the presence of test compound (the alleged allosteric effector) relative to the dissociation and/or association kinetics of the complex in the absence of said effector and/or determination of the variation in the amplitude of the bond formed between the receptor and one of its ligands in the presence or absence of potential effector. The claims do not recite a step of identifying a test compound detected by said methods as an allosteric effector. Thus, it is unclear if carrying out the method steps would result in accomplishing the goal set forth in the preamble.

Furthermore, Claim 1 is vague and indefinite in reciting “fluorescent proteins obtained or derived from autofluorescent proteins of cnidaria…..”. It is unclear how such proteins would be “derived”, i.e. whether “derived” means “’obtained from”, or is

somehow altered relative to what would be obtained from the organism; thus, the metes and bounds of the claim cannot be determined.

Claims 1- 3, 5, and 8-10 are vague and indefinite in reciting “amplitude of the bond..” The specification (page 10, lines 23-30) teaches "binding amplitude" designates the amplitude of the signal recorded, which is itself proportional to the level occupation of the receptor sites. It is thus unclear how a bond may have an “amplitude”, since the specification teaches amplitude of signal recorded. It is unclear if applicants intend strength of bond or number of bonds formed or something else entirely.

Claims 1 and 2 are vague and indefinite in reciting “variation in the above mentioned amplitude is negative”. Since the recitation of “amplitude of the bond” is vague and indefinite, the phrase “variation in the above mentioned amplitude is negative” is also unclear. It is unclear if applicants intend to indicate a decrease in binding of ligand to receptor or that the amplitude of the signal recorded is negative.

Claim 2 is vague and indefinite in reciting “one or more amino acids” without reciting an upper limit to the number of amino acids to be substituted.

It is unclear how Claim 3 further limits the method steps of Claim 1. Claim 3 is duplicative of Claim 1 in its’ recitation of determination of variation in the dissociation kinetics of the complex formed and/or in the amplitude of the bond formed between receptor and said ligand.

Claim 8 is grammatically incorrect and is therefore vague and indefinite. It is unclear what applicant intends by recitation of “by determination of…”. It is unclear if this is another method step, or is duplicative of method steps recited in claim 1.

Claims 9 and 10 appear to recite a desired outcome “said variation is positive” (Claim 9) and “said variation is negative” and not a method step that further limits the method of the instant invention.

Claims 11 and 12 recite desired results and not further the method steps.

Claims 4, 6 and 7 are included in this rejection as dependent upon rejected claims.

Claim interpretation:

Claim 1 and 2 are the independent claims of the instant invention.

Claim 1 is interpreted by the Examiner to be directed to a method of detecting an allosteric effector of a receptor comprising:

Determining variation in dissociation and/or association kinetics of complex formed by receptor and ligand in the presence of putative allosteric effector compared to dissociation/association kinetics of complex formed in absence of putative allosteric effector

And/or

Determining a change in the amount of ligand bound to receptor ("amplitude of the bond") in the presence of the test compound compared to that in the absence of the test compound is an indication that said test compound is an allosteric effector.

Said receptor being labeled with a fluorescent protein derived from autofluorescent proteins of cnideria

Said ligand labeled with a molecule capable of absorbing the light emitted by the fluorescent protein or a labeled with a fluorescent substance

Binding of the ligand to the receptor is determined using a fluorescence resonance energy transfer (FRET)-based assay in which detection of a change in dissociation and/or association kinetics and/or measuring a change in the amount of ligand bound to receptor ("amplitude of the bond") in the presence of the test compound compared to that in the absence of the test compound is an indication that said test compound is an allosteric effector.

Measuring dissociation and/or association kinetics as a means of evaluating ligand-receptor binding is well-known method in the art. "Amplitude of the bond" is interpreted as a measurement of ligand-receptor binding. One of ordinary skill in the art

would recognize that if there is a variation in receptor-ligand binding, there inherently would be a variation in association and/or dissociation kinetics.

Claim 2 is interpreted by the Examiner to be directed to a method of detecting an allosteric effector of a receptor comprising:

Determining variation in dissociation and/or association kinetics of complex formed by receptor and ligand in the presence of putative allosteric effector compared to dissociation/association kinetics of complex formed in absence of putative allosteric effector

And/or

Determining a change in the amount of ligand bound to receptor ("amplitude of the bond") in the presence of the test compound compared to that in the absence of the test compound is an indication that said test compound is an allosteric effector.

Said receptor being labeled with a fluorescent protein wherein the fluorescent protein is chosen from GFP, EGFP, CFP, ECFP, YFP, EYFP, or GFPUV

Said ligand being labeled with a molecule capable of absorbing the light emitted by the fluorescent protein or a labeled with a fluorescent substance

Binding of the ligand to the receptor is determined using a FRET-based assay in which detection of a change in dissociation and/or association kinetics and/or measuring a change in the amount of ligand bound to receptor ("amplitude of the bond") in the presence of the test compound compared to that in the absence of the test compound is an indication that said test compound is an allosteric effector.

Measuring dissociation and/or association kinetics as a means of evaluating ligand-receptor binding is well-known method in the art. "Amplitude of the bond" is interpreted as a measurement of ligand-receptor binding. One of ordinary skill in the art would recognize that if there is a variation in receptor-ligand binding, there inherently would be a variation in association and/or dissociation kinetics.

35 U.S.C. § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

It is noted that for purposes of prior art, priority is granted to 16 June 2003, the filing of PCT/FR03/01817

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ilien et al. (2003. Journal of Neurochem. 85:768-778, cited on IDS of 17 December 2004) in view of Christopoulos et al (2002. Physiol. Rev. 54:323-374).

Ilien et al teach an assay to study binding of ligand to human M1 muscarinic receptor. The assay comprises utilizing a human M1 muscarinic receptor (a G protein-coupled receptor or GRCR) chimera comprising enhanced green (or yellow) fluorescent protein (EGFP or EYFP) fused to a receptor N-terminus (receptor marked by a fluorescent protein chosen from autofluorescent proteins of cnidaria or chosen from EGFP or EYFP) and a fluorescent antagonist, pirzenzipene labelled with Bodipy [558/568] (Bo-PZ) (ligand marked by either a molecule capable of absorbing the light emitted by the fluorescent protein, or by a fluorescent substance) (abstract). FRET

monitoring of Bo-PZ binding properties to EGFP-M1 receptor was undertaken (page 773, 2nd column, 2nd paragraph, bridging page 774, 2nd column, 1st paragraph). The reference teaches plotting amplitudes of fluorescence extinction versus Bo-PZ concentration (page 774, 1st column, 2nd paragraph). Ilien et al teach kinetic determination of off-rate constants, thereby determining dissociation kinetics (page 776, 2nd column, 4th paragraph). Additionally, the reference teaches competitive binding assays comprising incublation of EGFP-M1 receptor, in the presence of increasing antagonist or agonist concentrations (test compound) together with Bo-PZ (page 774, 1st column, bridging 2nd column, 1st paragraph).

Ilien et al does not teach an assay comprising a labeled ligand wherein the labeled ligand is an agonist and a test compound which is a putative allosteric effector.

Christopoulos et al teach GPCRs are allosteric proteins (abstract). The reference further teaches that "clinically relevant allosteric modulators of GPCRs are viable and likely drug candidates" (page 354, 2nd column, 2nd paragraph). Christopoulos et al teach that allosteric modulators may be identified by studying allosteric modulator effects on radioligand kinetic binding properties (page 331, Figure 3B, 2nd column, 2nd paragraph and page 344, 2nd column, 1st paragraph) and on equilibrium binding (page 338, 2nd column, 3rd paragraph), which measures the amount of ligand bound to receptor ("amplitude of thebond"). One of ordinary skill in the art would know that the components of the radioligand binding assay as taught by Christopoulos et al. comprise labeled ligand, and receptor (analogous to the labeled ligand and receptor taught by Ilien et al) and test compound (putative allosteric modulator).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the methods taught by Ilien et al. comprising utilizing a human M1 muscarinic receptor (a G protein-coupled receptor or GPCR) chimera comprising enhanced green (or yellow) fluorescent protein (EGFP or EYFP) fused to a receptor N-terminus and a fluorescent antagonist, pirzenzipene labelled with Bodipy [558/568] (Bo-PZ) and utilize said method to screen for allosteric modulators of GPCRs as taught by Christopoulos et al. The person of ordinary skill in the art would

have been motivated to make these modifications and would have anticipated success because Christopoulos et al teach using receptor ligand binding assays to screen for allosteric modulators of GPCR signaling and that said identified modulators would be useful as drug candidates. One is always motivated to identify new drug candidates for treating disease. Additionally, one of ordinary skill in the art would recognize that receptor binding assays may be performed with either labeled antagonists (as taught by Ilien et al.) or labeled agonists

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klein et al (US 7,319,009, issued 15 January 2008, priority claimed to SSN 09/201,396, filed 30 November 1998 and PCT/US98/21168, filed 7 October 1998, the '009 patent) in view of Pollok et al. (1999. Trends in Cell Biol 9:57-60) and further in view of Christopoulos et al (2002. Physiol. Rev. 54:323-374). The '009 patent teaches methods of screening and identifying pharmaceutically effective compounds that interact with and modulate the activity of a cellular receptor or ion channel. The reference specifically teaches assays comprising the human formyl peptide receptor like-1 (FPRL-1) receptors, a GPCR (abstract). The '009 patent teaches that receptor binding assays may be performed using FRET methodologies. The target FPRL-1 receptor protein is labeled with a first fluorescent indicator molecule and the ligand agonist of the FPRL-1 receptor is labeled with a second fluorescent indicator molecule. Fluorescence resonance energy transfer (FRET) can occur when the first and second indicator molecules are in close proximity to each other. Assays using FRET are known to one of skill in the art (column 23, lines 7-14). The reference teaches a test compound that antagonizes the interaction between a target FPRL-1 receptor protein labeled with a first fluorescent indicator molecule and a ligand agonist labeled with a second fluorescent indicator molecule can also be detected using FRET (column 23, lines 30-35). The method taught by the '009 patent comprising a labeled receptor, labeled ligand and test compound can be used to identify a modulator of the FPRL-1 receptor (column 23, lines 46-48).

The '009 patent does not teach a method comprising a receptor specifically labeled with a fluorescent protein derived from autofluorescent proteins of cnideria or a receptor specifically labeled with GFP, CFP or ECFP, YFP or EYFP, GFPUV, and a test compound which is a putative allosteric effector, nor a labeled ligand wherein the ligand is an antagonist, and does not teach specific methods of detecting allosteric effect (i.e. detecting variation in dissociation and/or association kinetics of the complex formed or variation in amplitude of the bond formed).

Pollok et al teach the use of fusion proteins comprising GFP in FRET assays (page 59-page 60, 1st column, 1st paragraph). Christopoulos et al teach GPCRs are allosteric proteins and that allosteric sites on GPCRs represent novel drug targets (abstract). The reference further teaches that "clinically relevant allosteric modulators of GPCRs are viable and likely drug candidates" (page 354, 2nd column, 2nd paragraph). Christopoulos et al teach that allosteric modulators may be identified by studying allosteric modulator effects on radioligand kinetic binding properties (Figure 3B, page 331, 2nd column, 2st paragraph and page 344, 2nd column, 1st paragraph) and radioligand binding assays, a measurement of the amount of ligand-receptor binding (which measure the "amplitude of the bond"). One of ordinary skill in the art would recognize that the components of the radioligand binding assay comprise labeled ligand and receptor (analogous to the ligand and receptor taught by the '009 patent) and test compound (putative allosteric modulator).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the GPCR labeled with a fluorescent indicator protein as taught by the '009 patent and substitute GFP, as taught by Pollok et al. for the generic "fluorescent indicator protein" taught by the '009 patent; additionally, it would be *prima facie* obvious to use this GFP-labeled protein in a modification of the methods taught by the '009 patent (comprising FRET receptor-ligand binding assays) and utilize said method to screen for allosteric modulators of GPCRs as taught by Christopoulos et al. The person of ordinary skill in the art would have been motivated to make these modifications and would have anticipated success because Pollok et al

teach the use of GFP labeled proteins in FRET assays and Christopoulos et al teach using receptor ligand binding assays to screen for allosteric modulators of GPCR signaling and that said identified modulators would be useful as drug candidates. One is always motivated to identify new drug candidates for treating disease. Additionally, one of ordinary skill in the art would recognize that receptor binding assays may be performed with either labeled agonists (as taught by the '009 patent.) or labeled antagonists

Conclusion:

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao, Ph.D. can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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